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SPECIAL COMMUNICATION

Misoprostol for postpartum hemorrhage: Moving from evidence to practice

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ABSTRACT

Clinical and operational evidence indicates that misoprostol is a safe and effective technology for addressing postpartum hemorrhage, a major cause of maternal death. This research has not yet been translated into effective policies, programs, and practice in many parts of the world. Efforts to expand evidence-based use of misoprostol are often complicated by misoprostol's range of indications, insufficient availability, a lack of evidence-based guidelines and provider training, and misconceptions about the drug. The medical and health policy communities need to work together to translate research findings into changes in policy, knowledge, and clinical practice so that we can deliver on the world's promise to improve maternal health.

1. Introduction

As the global community strives to deliver on Millennium Development Goal (MDG) 5's promise to improve maternal health, evidence is growing of misoprostol's value in addressing the global burden of postpartum hemorrhage (PPH), the leading cause of maternal death in low-resource regions of the world. In March 2011, misoprostol was added to the WHO Model List of Essential Medicines for the prevention of PPH, validating its important role for women's health and survival [1]. Misoprostol has also been added to many global and national clinical guidelines (such as FIGO/ICM [2], ACOG [3], and RCOG [4], among others) for addressing PPH. These developments reflect a growing consensus that misoprostol is a safe and effective option for preventing and treating PPH, particularly in settings where oxytocin—the gold standard drug—is not available or where its administration is not feasible.

Emerging research has provided compelling evidence of misoprostol's potential to prevent and treat PPH, and has established its safety and efficacy, and its acceptability to women. We now know that:

- Oral misoprostol (600 μg) can be safely and effectively administered by lower-level health providers to prevent PPH [5,6].
- Sublingual misoprostol (800 μg) is a safe and effective treatment for women experiencing PPH [7,8].
- Adjunct use of misoprostol (i.e. simultaneous treatment with misoprostol in addition to oxytocin) provides no additional benefit for women who are receiving oxytocin to treat PPH and results in increased adverse effects [9].
- Misoprostol has the potential to address coverage gaps and provide logistical advantages in both facility and community settings (Box 1).

However, this growing body of research has yet to be translated into effective policies, programs, and practice in many parts of the world. We have the evidence. Our challenge now is to use the evidence of misoprostol's efficacy and safety to ensure that every woman has access to a uterotonic for prevention and/or treatment of PPH.

Efforts to broaden women's access to misoprostol face significant and unique challenges. In contrast to the situation with new pharmaceutical products, the widespread introduction of misoprostol is both facilitated and complicated by the drug's history and the policy environments that govern its use. Because it has been used *ad hoc* for over 30 years, many providers have experience with misoprostol. Those who have used it safely and effectively in the past are often highly supportive of its wider use; those who have witnessed its misuse—for example, the administration of dangerously high dosages for induction of labor—may take a more negative view. Furthermore, misoprostol's effectiveness for a variety of indications (Box 2) can provide opportunities for its wide-scale adoption, but may also (particularly in terms of its association with abortion) engender discomfort and resistance among policy makers and providers, and outright opposition from antiabortion activists. Lastly, as misoprostol is not a new drug, it may benefit from existing pathways to introduction, but must also overcome a history of controversy.

2. Challenges to evidence-based use of misoprostol

2.1. Use for a range of indications

Misoprostol has a range of uses and indications in reproductive health (Box 2). In some parts of the world, this potential has resulted

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Box 1
Advantages of misoprostol.

- Stable at room temperature
- Easy to store and administer
- Inexpensive
- Widely available

Box 2
Women's heath indications for misoprostol.

- Cervical priming
- Induced abortion
- Labor induction
- Uterine evacuation after failed pregnancy
- Prevention and treatment of PPH

in increased sensitivity and controversy related to possible "misuse." Misoprostol's use as an abortifacient and the incorrect, mistimed, or overly aggressive use of misoprostol for inducing labor have often stymied efforts to promote its use for PPH.

It is important that practitioners, policy makers, and advocates work together to ensure that concerns about misoprostol's use for other indications do not lead to limitations on its availability for PPH.

2.2. Availability and registration of misoprostol

Considerable attention has been focused in the past few years on registering misoprostol specifically for the prevention and/or treatment of PPH, as a step toward increasing its availability for PPH. However, registration for a specific use is neither necessary nor sufficient to ensure availability for that medical condition. Indeed, "not registered" is not equivalent to "inappropriate," "dangerous," or "ineffective." Many drugs are not registered for indications for which there is substantial evidence of safety and effectiveness. "Not registered" simply means a marketing agreement is not in place permitting promotion and sale of the drug for that particular indication. Off-label use is common and is sanctioned by stringent regulatory agencies in many parts of the world as an effective way for providers to follow evidence-based practices. Furthermore, governments are not beholden to commercial registration and can choose to make a product available if it has a public health benefit.

While pursuing registration may in some cases be a useful strategy for increasing availability of misoprostol, the importance of this strategy depends on the context. In some countries, no misoprostol products are registered, yet it is widely available; conversely, in other countries there are registered products that cannot be found on any pharmacy shelves. In many countries, misoprostol is commercially registered only for its original indication of preventing gastric ulcers; often, this product can be used off-label for PPH. Whether or not pursuing registration specifically for PPH is necessary depends on government policies and regulations in each country. Advocacy to improve the availability of misoprostol on a national level may involve pursuing registration, promoting inclusion on the national essential medicine list, both, or neither; it is important to bear in mind that the utility of each of these steps is context specific. [10]

2.3. Lack of evidence-based guidelines and provider training

A product's availability does not ensure its appropriate use. When labels for registered products do not reflect the current evidence, clinical guidelines can correct for this problem by gathering, interpreting, and disseminating emerging evidence. Unfortunately, national clinical guidelines are often slow to reflect the latest research, hampering efforts to provide the most effective evidence-based health care. This is an issue particularly with regard to misoprostol due to the dearth of clear and consistent usage guidance. As a result, misoprostol is often used with outdated, nonevidence-based protocols.

Evidence-based guidelines for the use of misoprostol for PPH need to be put in place at the national level, and this must be supplemented by training and ongoing education of providers. Since this drug can be used for multiple indications, training must include clear dosing information, including the routes and precautions associated with each type of use.

2.4. Misconceptions and misperceptions

There remain concerns, often unsupported by available evidence, about misoprostol's distribution and use at the community level and with home deliveries. Some policy makers worry that promotion of misoprostol for use in nonfacility deliveries may deter women from seeking care at facilities with skilled providers. In a world where barely half of women in low-resource countries give birth with a skilled attendant, these concerns—while understandable—ignore the harsh reality faced by women in low-resource settings: that skilled, facility-based childbirth care is often not accessible. In seeking to ensure that all women—regardless of where they give birth—have access to uterotonics for prevention and treatment of PPH, countries should be supported in pursuing complementary, mutually-supportive strategies. For example, the government of Nepal's strategy for preventing PPH is to promote active management of the third stage of labor in facilities and the use of misoprostol at home births. More evidence on the impact of community distribution of misoprostol on rates of facility-based delivery will be useful, but it is important that the goals of protecting women's lives and health from uncontrolled hemorrhage and of providing skilled care for every woman are not placed in conflict with one another. Rather, policies and practices must approach these issues as complementary.

There are also perceptions that, if misoprostol is made more widely available for use with PPH, it will be repurposed for use in medical abortion, thereby increasing the number of abortions. Based on these fears—which are unsupported by the evidence—policy makers in some countries have placed restrictions on misoprostol's availability. In some Latin American countries, for instance, only physicians are legally permitted to prescribe misoprostol. Because a large number of deliveries are attended by nurses and midwives, this policy either limits women's access to medicines they need to protect their lives and health, or it creates a direct conflict between law and clinical practice. Those who wish to restrict women's right to reproductive choice should not be permitted to limit access to a safe, effective, and practical drug for managing PPH.

Experience has shown that obstetricians and gynecologists can be particularly compelling advocates on these issues. In countries where advances in community-level access to misoprostol offer the promise of reducing mortality and morbidity from PPH, national obstetrics and gynecology associations have played an important advocacy role. Recognizing the current undersupply of skilled physicians, as well as the lack of well-equipped facilities offering basic and advanced obstetric care, physicians have been leaders in efforts to develop innovative and effective ways of ensuring universal access to uterotonics. [11]

3. Strategies for expanding access to evidence-based care

3.1. Disseminate research

Transforming research findings into effective changes in policy, knowledge, and clinical practice requires a number of mutually-reinforcing strategies:

- Identifying champions, who can share research with a broad range of audiences and influence policies, future research, facility-level clinical practice, and clinicians' behavior.
- Providing regular technical updates, through workshops, publications, and other mechanisms to share the latest scientific information and evidence.

3.2. Share experiences

Country-to-country exchange of experience is crucial for addressing misconceptions related to increased access to and use of misoprostol. Results of research, operations studies, or pilot programs conducted in one country can, if shared effectively, have a positive influence in many others. It is thus important to share experiences and best practices at the regional level.

3.3. Engage professional associations as partners

Professional associations, including obstetrics/gynecology and midwifery societies, are key partners in providing accurate information about the use of misoprostol for PPH to policy makers and other stakeholders. Giving health providers (including midlevel/community providers) accurate, updated information will help to ensure that all women receive high-quality maternal health care. A good example of professional leadership is the 2011 Special Editorial published in the IJGO by FIGO Chief Executive Professor Hamid Rushwan, which calls attention to misoprostol's importance for PPH and the related work FIGO plans to undertake [12]. FIGO is a key partner of an initiative led by Gynuity Health Projects to develop and translate evidence on the role of misoprostol in PPH prevention and treatment.

4. Conclusion

Misoprostol has emerged as a promising technology for addressing the global burden of PPH; however, we must remember that it is not a panacea. No drug can replace the need for strengthened basic and emergency obstetric care services; for more and better-trained health workers; for clean, well-equipped facilities; and for culturally-sensitive, high-quality maternal health care. Rather, misoprostol must be viewed as one strategy among many—albeit one that can help to address some of the stubborn challenges faced by health systems and facilities that still lack consistent electricity, cold storage, trained providers, and/or intravenous therapy. As we work together to reduce the suffering and mortality caused by PPH around the world, we should keep our ultimate goal in sight: ensuring that every woman has access to a uterotonic for effective management of PPH; that every woman can benefit from advances in medical technology and knowledge; and that every woman receives the skilled, high-quality obstetric care that is her right and the world's obligation.

Conflict of interest

The authors declare that no conflicts of interest exist.

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